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Research Article

The Beneficial Effect of Paricalcitol (Zemlar) on Secondary hyperparathyroidism Refractory to Calcitriol (Calcijex) and Cinacalcet HCl (Mimpara) in Patients on Maintenance Hemodialysis: A Prospective and Crossover Study

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ABSTRACT

Paricalcitol, 19-nor-1, 25-dihydroxyvitamin D₂, is a novel 1,25-dihydroxyvitamin D₂ analogue, which has greater potential to suppress parathyroid hormone without inducing significant hypercalcemia and hyperphosphatemia. We therefore investigated its role in treatment of patients with moderate to severe secondary hyperparathyroidism (SHPT) who were refractory to conventional therapy with Calcitriol and Cinacalcet HCl. Eight patients were recruited in whom conventional therapy was stable over the past 3 months. After a washout period of 2 weeks, calcijex injections were replaced by Paricalcitol. Paricalcitol induced more suppression of iPTH compared to the conventional therapy without significant hypercalcemia, hyperphosphatemia or side effects. The conversion ratio was approximately 1:2.5 (calcitriol:paricalcitol). In conclusion, injectable Paricalcitol is superior to Calcitriol in treatment of SHPT.

Keywords: Cinacalcet, Calciferol, hemodialysis, hyperparathyroidism, Paricalcitol.

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INTRODUCTION

Disturbances in mineral and bone metabolism are common in patients with chronic kidney disease [1]. They include; hyperphosphatemia due to decrease excretion through the failing kidney, hypocalcemia due to decline in the gut absorption due to decline in the conversion of 25 hydroxyvitamin D to its potent 1,25 dihydroxy version and lastly the activation of parathyroid gland in its attempt to correct hyperphosphatemia. The parathyroid gland is also affected by the declining levels of serum calcium and vitamin D in addition to altered set-point of serum calcium leading to more hyperplasia, secretion and further damage [2]. With the declining kidney function mineral abnormalities produce osteomalacia (decreased bone calcification) and/or secondary hyperparathyroidism (osteitis fibrosa cystica) with increased risk of fractures, bone deformities, bone cysts, osteopenia, resistance to erythropoietin, intractable prurities, spontaneous tendon rupture, periarthritis, myopathy, growth failure in children and extraskeletal

calcification [3]. Moreover, secondary hyperparathyroidism has been recognized as a uremic toxin via increasing the intracellular calcium, resulting in disturbances in the function of virtually every organ system [4]. Unfortunately, treatment of moderate cases of SHPT with calcium-containing phosphate binders and the available vitamin D analogues viz. One alpha (1 hydroxyvit D) and Calcitriol (1,25 dihydroxyvit D), though useful and equivalent [5], has been associated with hypercalcemia [6]. Furthermore, hyperphosphatemia was noted to be more difficult to control with Calcitriol and one alpha due to enhanced gut absorption and release through enhanced bone resorption [7]. Such hypercalcemia with or without high Ca²⁺ product has been recently recognized as a risk factor for visceral and vascular calcification which was linked to increased morbidity in dialysis patients [8]. Cinacalcet HCl (Mimpara) has been introduced recently into the field and had an impressive suppression of the parathyroid gland [9]. However, its gastrointestinal side effects limited its use. Paricalcitol, 19-nor-1,25-dihydroxyvitamin D₂, is a new analogue of

ergocalciferol which appears to have the same suppressive effect on SHPT, but with less direct effect on the gut and bone. Crossover studies evaluating its efficacy over the treatment with the conventional therapy of IV Calcitriol (Calcijex) and Mimpara are essential to overcome the interpatient variability in response to such therapy. This pilot study was conducted to answer the latter questions.

PATIENTS AND METHODS:

This prospective open-label crossover study was performed at Edeliah dialysis center which is responsible for the care of nearly 360 patients residing in the capital area of Kuwait. All patients are receiving maintenance hemodialysis three times weekly with a dialysate calcium concentration of 2.5 mmol/L. All patients are receiving regularly nutritional counseling that limits their phosphorus intake to 1 g/day and calcium to 2 g/day. Calcium supplementation with/without non-calcium containing phosphate binders sevelamer (Renvella; Genzyme Corp, Cambridge, MA) are given to lower phosphorus level to acceptable range (< 1.78 mmol/L) and keep calcium levels at the upper limit of normal (2.37 mmol/L) yet avoiding CaXP product above 4.22.

Selection criteria:

Patients with persistent moderate to severe SHPT (iPTH > 30 pmol/L) for at least 3 months despite treatment with calcijex and cinacalcet were identified. However, only those who were stable medically, socially and psychologically were selected to ensure compliance with diet and medications.

Exclusion criteria:

Patients were excluded from the study if they had history of allergic reaction to calcitriol or other vitamin D analogues, a current malignancy, clinically significant liver disease, a history of drug or alcohol abuse within the last 6 months, or evidence of blood-borne infections such as hepatitis or HIV. None of the patients recruited had enlarged parathyroid gland on ultrasonography or positive activity on parathyroid subtraction nuclear scan.

Crossover to paricalcitol:

Calcitriol was discontinued for 2 weeks prior to starting paricalcitol. Paricalcitol therapy was initiated by converting patients from Calcitriol therapy to Paricalcitol at a starting dose of 2.5-5 ug after each dialysis session. Further adjustment in calcium and phosphate supplementation as well as Paricalcitol and Cinacalcet doses, were determined at the discretion of the treating physician to achieve better suppression of parathyroid hormone level. Patients were followed up for 3 months in both stages with a 2 weeks period of wash out. For the sake of the study, corrected serum calcium, phosphorus, alkaline phosphates were measured every 2 weeks. Parathyroid hormone was measured by means of an intact hormone radioimmunoassay.

RESULTS

Initially, 10 patients were included on the study and were observed for 3 months on the conventional therapy. However, by the end of the first phase, 2 had to be excluded for non-compliance with their oral medications. Demographical data and the ancillary therapy received during the 2 phases of treatment are included in Table.1. Changes in corrected calcium, phosphorus, alkaline phosphatase and iPTH during the 2 phases of the study are presented in Table.2. As shown in Table.2, 7 patients had inadequate response to the conventional therapy with

Calcitriol and Cinacalcet with iPTH levels above 33 pmol/L and one patient could not tolerate Calcitriol due to hypercalcemia.

Starting point:

Levels of iPTH and alkaline phosphatase increased at the end of washout period.

Paricalcitol phase of treatment:

All patients experienced more suppression of iPTH and had reached the target iPTH (≤ 33 pmol/L).

Interpatient variation of response:

Assessment of individual patients showed the following:

- 1- Patient 1 showed adequate response at a conversion ratio of 1:2.5.
- 2- Patient 2 showed favorable response yet the dose of Paricalcitol had to be increased up to 5 ug 3 per week i.e. a conversion ratio of 1:5.
- 3- Patient 3 was on 60 mg daily of Cinacalcet and his serum calcium was 2.41 mmol/L, low phosphorus (0.72 mmol/L) and low CaXP product despite absence of P-binders. Interestingly, Paricalcitol treatment was not associated with worsening of hypercalcemia yet serum P improved to normal with improvement of his SHPT.
- 4- Patient 4 required 5ug thrice weekly of Paricalcitol in the first 2 months yet the final maintenance dose was in accordance with a 1:2.5 conversion ratio.
- 5- Patient 5 who already could not tolerate vitamin D analogue due to hypercalcemia, tolerated Paricalcitol without significant drop in his iPTH.
- 6- Patient 6 & 7 had low calcium levels during the second month that responded to temporary discontinuation of cinacalcet. By that, iPTH level had dropped from 86 to 64 pmol/L in the first patient and 72 to 46 in the second. Reintroduction of Cinacalcet in the last month at a lower dose (30 mg every other day resulted in further decline in iPTH to the target level without hypocalcemia.
- 7- Patient 8 had high P and serum calcium at the upper limit of normal. The initial conversion ratio for Calcitriol to Paricalcitol was 2:2.5. However, at later weeks paricalcitol dose had to be increased to 5 ug without further worsening of hypercalcemia or hyperphosphatemia to achieve the target iPTH level.

Safety and adverse side effects:

- 1- Paricalcitol therapy was not associated with significant hypercalcemia, hyperphosphatemia or high CaXP product.
- 2- None of the patients treated with Paricalcitol had experience significant allergic reaction to the IV medication, cardiovascular instability or GI side effects.

DISCUSSION

The safety of and efficacy of Paricalcitol in treatment of SHPT with less hypercalcemia and hyperphosphatemic side effect have been established for many years [10]. Moreover, an animal study has shown that the drug did not increase aortic calcium content in animals compared to Calcitriol [11]. In fact, the meeting of the WHO International Working Group for Drug Statistics Methodology in 24th March 2009 reclassified Paricalcitol from being simply another vitamin D

analogue to an anti-parathyroid drug and has been given the new code (H05BX02). Comparative studies against cost-effective analysis [13]. Interestingly, cross-over studies comparing Calcitriol and Paricalcitol essential to overcome the interpatient variability of response to both drugs are limited to 3 only. The first study compared the shift from Calcitriol treatment to Paricalcitol in 73 patients on maintenance hemodialysis and patients were followed for 6 months [14] while the second recruited 59 patients for one year [15]. Both investigators admitted that some of their patients missed fewer doses of Paricalcitol. The third and more recent study recruited 12 patients who were followed for one year [16]. In our study, we added the factor of using the available maximal conventional therapy not only with Calcitriol but with Cinacalcet. Our study showed that iPTH levels were significantly reduced with amelioration of the previous hyperphosphatemia and hypercalcemia noted in the previous phase of the conventional therapy. This phenomenon may have been related to the vitamin D receptor selectivity of the chemically produced Paricalcitol being only on the parathyroid gland compared to the naturally produced Calcitriol. The latter effect may be desirable for normal people and renal patients with osteomalacia and hypocalcemia but not for patients with already advanced stage of SHPT. Moreover, such an effect is shown in our study to be an additive one to the calcimimetic effect of Cinacalcet since it acts differently via improving the calcium-sensing receptors located on the surface of the chief cells of the parathyroid gland [17]. In our study, the dose conversion ratio from Calcitriol to paricalcitol is nearly 1:2.5 rather than 1:3 reported earlier [14-16]. This issue is practically useful since the ampoule of Calcitriol contains either 1 or 2 ug while that of Paricalcitol is 5 ug/ml.

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Table.1 Demographic data and therapy before and after conversion of injectable calcitriol (calcijex) to paricalcitol (zemplar)

Patient number	age (years)	Sex	TRD	Durtion on HD (years)	Phases of treatment	Ancillary treatment					
						Calt-0	Calat-3	Renv-0	Renv-3	Mimp-0	Mimp-3
1	57	M	Diabetic	4.5	Calcijex	1gX3	1gX3	800mgX2	800mgX2	30mg/d	30mg/d
					Zemplar	1gX3	1gX3	800mgX3	800mgX2	30mg/d	30mg/d
2	46	M	Chronic GN	2.5	Calcijex	1gX3	1gX3	No	No	30mg/d	30mg/d
					Zemplar	1gX3	1gX3	No	No	30mg/d	30mg/d
3	79	F	Nephroangiosclerosis	7	Calcijex	1gX3	1gX3	No	No	60mg/d	60mg/d
					Zemplar	1gX3	1gX3	No	No	60mg/d	60mg/d
4	61	F	Nephroangiosclerosis	3	Calcijex	1gX3	1gX3	800mgX3	800mgX3	30mg/d	30mg/d
					Zemplar	1gX3	1gX3	800mgX3	800mgX2	30mg/d	30mg/d
5	66	F	Diabetic	5	Calcijex	No	No	800mgX3	800mgX3	30mg/d	30mg/d
					Zemplar	No	No	800mgX3	800mgX3	30mg/d	30mg/d
6	70	M	Chronic GN	3	Calcijex	1 gX2	1 gX2	800mgX3	800mgX3	30mg/d	30mg/d
					Zemplar	1 gX3	1 gX3	800mgX3	No	30mg/d	15mg/d
7	73	F	Chronic tubulointerstitial	13	Calcijex	No	No	800mgX3	800mgX3	30mg/d	30mg/d
					Zemplar	1gX3	1gX3	800mgX3	800mgX3	30mg/d	15mg/d
8	25	F	Chronic GN	2.5	Calcijex	1gX2	1gX2	800mgX3	800mgX3	60mg/d	60mg/d
					Zemplar	1gX3	1gX3	800mgX3	800mgX3	60mg/d	60mg/d